An Unprecedented Ring Transformation of a 4-(Aminomethyl)oxazoline Derivative to a 4-(Hydroxymethyl)imidazoline

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Abstract: An optically active 4-(azidomethyl)-2-(2-pyridyl)oxazoline was prepared starting from L-serine and picolinic acid. Reduction of the azide moiety gave the corresponding 4-(aminomethyl)-2-(2-pyridyl)oxazoline, which is not a stable compound but readily undergoes ring-transformation rearrangement to furnish a 4-(hydroxymethyl)-2-(2-pyridyl)imidazoline. After Boc protection of the amidine function, the material could be further converted into the 4-(aminomethyl)-2-(2-pyridyl)imidazoline via the respective azidomethyl compound.

Key words: heterocycles, oxazolines, imidazolines, pyridines, chiral ligands

Since the first reports by Brunner and co-workers,1 optically active 2-pyridyloxazolines have become a privileged class of chiral ligands in asymmetric catalysis.2,3 In continuation of our earlier work on C3-symmetric, tridentate pyridyloxazolines,4 we were planning to prepare compound 1 with an aminomethyl group, the latter being perfectly suited for further N-functionalization, for example by amidation reactions. In the event, we were unable to isolate compound 1, nor its derivatives, as it always underwent ring transformation to furnish the hydroxymethyl-functionalized pyridylimidazoline 2 (Scheme 1). Such a ring transformation has been reported once before for the formation of a cyclic urea from a urethane.5 It has been at least suspected for [(N-arylamino)methyl]oxazolines,6 but not observed by others, although some researchers claim to have isolated an (aminomethyl)oxazoline as an intermediate product.7 In one other case, an in situ formed (aminomethyl)oxazoline was protected with CbzCl in the reaction mixture.8 Since optically active imidazolines are an increasingly important, novel class of chiral ligands,9 investigations on further conversion of the product 2 seemed promising to us. Therefore, we now report on the preparation of compound 1 and its transformation to imidazoline 2, as well as some further chemistry starting with the latter compound.

The starting point of our investigation was the hydroxymethyl compound 7, which was obtained by the five-step sequence outlined in Scheme 2. Picolinic acid (3) was first coupled with methyl L-serinate10 to give amide 4 (71%).11 The primary alcohol was then TBS protected (92% yield of compound 5)12 and the ester moiety reduced to again give a primary alcohol 8 (79%), which was activated with tosyl chloride and cyclized according to a literature protocol.13 Intermediate product 6 (77%) was finally deprotected with tetrabutylammonium fluoride (93% yield of product 7).

Organooazides are excellent precursors for primary amines; therefore, we activated the primary alcohol function of compound 7 by sulfonyl ester formation (95% of product 9) and converted it with sodium azide in ethanol following common protocols (Scheme 3).14 Product 10, after chromatography, was obtained in almost quantitative yield. Azide 10 was subjected to catalytic hydrogenation to again give a single compound (95% yield) with correct mass (ESI) and 1H and 13C NMR spectra that seemed to be in agreement with structure 1; however, all attempts at further derivatization of what we assumed to be an amino function, in particular amide formation, failed. We realized that the ring-transformation reaction of intermediate product 1 with formation of imidazoline 2 would be an explanation for our failure to produce amides of purportedly similar structure.
amine 1. Imidazoline 2 would give similar $^1$H and $^{13}$C NMR spectra, leading us astray. This rearrangement appears obvious, since the amino group as a good nucleophile is at the right distance to form a bicyclo[2.2.1] intermediate structure when adding to the electrophilic imidoester group.

Definite proof of the structure of compound 2 came from its subsequent chemistry, which was initially difficult as the very basic amidine function caused several problems with chemoselectivity. These problems could, however, be solved by reducing the electron density of 2 by installing a carbamate function (product 11, 67% yield of crude material; Scheme 4). Interestingly, we obtained a single compound, although one would expect a regioselectivity problem due to the presence of two nucleophilic nitrogen atoms at the amidine function. The depicted regiochemistry was proven by 2D-NMR spectroscopy, after the assignment of all resonances. Firstly, C-4 and 4-H were identified by DEPT135 and HMQC experiments [$\delta^{(13)}$C = 66.8, $\delta^{(1)}$H = 4.28 ppm]. Furthermore, the pyridine signals were identified by H,H-COSY and HMQC experiments, as follows [$\delta^{(1)}$H, $\delta^{(13)}$C, in ppm]: 7.5 (3'-H), 123.4 (C-3'); 7.7 (4'-H), 136.3 (C-4'); 7.29 (5'-H), 124.3 (C-5'); 8.58 (6'-H), 148.6 (C-6). The quaternary pyridine C-2' was then identified at 151.4 ppm (HMBC cross peaks with 6'-H and 4'-H). Of the two remaining sp2-carbon resonances, the amidine C-2 was assigned at $\delta$ = 159.4 ppm by the HMBC cross peak with 3'-H. Therefore, the carbamate C=O must be the remaining sp2 signal at $\delta$ = 150.4 ppm. The two methylene protons 5-H were then identified at $\delta$ = 3.84 and 3.99 ppm by the HMBC cross peak with the amidine C-2; the respective C-5 was identified at $\delta$ = 49.3 ppm (HMQC experiment). The remaining 4-CH$_2$OH was identified at $\delta^{(1)}$H = 3.64 and 3.74 ppm, and $\delta^{(13)}$C = 64.3 ppm (HMQC experiment). With this assignment of all proton and carbon resonances in hand, the structure of compound 11 was finally proven by $^{15}$N,H-HMBC spectroscopy; three $^{15}$N signals were observed, and were assigned according to the literature data for a similar 1-acetyl-2-aryl-4,5-dihydroimidazole.$^{15}$ $\delta^{(15)}$N = –74.1 (N-1'), –122.8 (N-3), –244.5 (N-1) ppm, with MeNO$_2$ ($\delta$ = 0) as external standard. Naturally, within the pyridine ring, N-1' showed cross peaks to 3'-H, 5'-H and 6'-H. The carbanate N-1 showed three strong cross peaks, to 4-H and both 5-H protons, whereas the imine N-3 showed two strong cross peaks, to both 4-CH$_2$OH protons, and one weak cross peak, to one 5-H proton.

The alcohol function of 11 could then be activated by tosylate formation (40% yield of product 12) and subsequently be displaced with azide to furnish compound 13 (73% yield). Finally, the aminomethyl compound 14 was obtained by hydrogenation of azide 13 (67% yield), and actually represents the N-Boc-imidazoline congener of our initial target compound 1. This material 14 will now be the cornerstone in future efforts for the synthesis of new libraries of chiral polydentate ligands.

In summary, during our studies towards new, optically active tridentate ligands, we considered aminomethyl-substituted pyridyl/imidazoline 1 as a core structure which would be ready for further derivatization at the primary amino function. However, attempts to prepare target compound 1 by reduction of the respective azidomethyl precursor 10 directly led to the rearranged product 2 with a hydroxymethyl-substituted imidazoline ring. This very basic amidine moiety hindered subsequent chemistry and was therefore protected with a tert-butyloxycarbonyl group. It was then possible to access the (aminomethyl)(pyridyl)imidazoline 14 which is now ready for further diversifying derivatization at the primary amino function.

Preparative column chromatography was carried out using Merck silica gel (35–70 µm, type 60 A) with hexane, EtOAc and MeOH as eluents. The column dimensions are given as follows: diameter $\times$ height. TLC was performed on Merck aluminum plates coated with silica gel F$_{254}$, $^1$H and $^{13}$C and $^{15}$N NMR spectra were recorded on a Bruker Avance DRX 500 instrument. Multiplicities of carbon signals were determined with DEPT experiments. MS and HRMS spectra were obtained with a Waters Q-Tof Premier (ESI) spectrometer. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a Golden Gate diamond ATR unit. Elemental analyses were determined with a Euro EA-CHNS instrument from HEKATech. Optical rotations were measured with a PolaraTech M polarimeter from Schmidt and Haensch. Methyl L-serinate hydro-
chlordane was prepared according to a literature procedure. All other starting materials were commercially available.

Methyl (3)-N-(2-Pyrindylcarbonyloxy)serinate (4)  
N-Methylmorpholine (10.3 mL, 9.46 g, 93.5 mmol) and ethyl chloroformate (4.20 mL, 4.85 g, 44.7 mmol) were added to an ice-cooled suspension of picolinic acid (3) (5.00 g, 40.6 mmol) in anhydrous THF (50 mL) and the mixture was stirred for 0.5 h at this temperature. Methyl 1-serinate hydrochloride (7.00 g, 44.7 mmol) was added and, after further stirring for 2 h at r.t., the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and H2O (50 mL), and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (MgSO4) and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 7 cm × 11 cm; EtOAc–hexane, 2:1, Rf = 0.25) to yield compound 4 (6.46 g, 28.8 mmol, 71%) as a colorless liquid. All spectroscopic data were in accordance with the literature.11

IR (ATR): 3384 (m), 2955 (m), 2931 (m), 2885 (w), 2859 (m), 1666 (s), 1593 (w), 1521 (s), 1466 (m), 1436 (m), 1391 (w), 1363 (w), 1293 (w), 1255 (m), 1091 (s), 1046 (m), 1022 (m), 1000 (m), 940 (w), 835 (s), 779 (cm⁻¹).

1H NMR (500 MHz, CDCl3):  δ = 0.04 (s, 3 H), 0.07 (s, 3 H), 0.86 (s, 3 H), 3.95 (s, 3 H), 3.99 (dd, J = 10.1, 3.5 Hz, 1 H), 4.19 (dd, J = 10.1, 3.5 Hz, 1 H), 4.86 (dt, J = 8.6, 3.2 Hz, 1 H), 7.43 (dd, J = 7.6, 4.5 Hz, 1 H), 7.84 (td, J = 7.7, 1.7 Hz, 1 H), 8.18 (dt, J = 7.6, 1.1 Hz, 1 H), 8.60 (dd, J = 4.8, 1.6, 0.8 Hz, 1 H), 8.74–8.78 (m, 1 H).

13C{1H} NMR (125 MHz, CDCl3): δ = –5.6 (CH3), –5.4 (CH3), 18.3 (C), 25.8 (3 CH3), 52.5 (CH2), 54.6 (CH3), 63.8 (CH2), 122.4 (CH), 126.4 (CH), 137.3 (CH), 148.5 (CH), 149.7 (C), 164.3 (C), 170.9 (C).


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\( ^1H \) NMR (500 MHz, CDCl\(_3\)): \( \delta = 3.18 \) (s, 1 H), 3.70 (dd, \( J = 11.6, 4.0 \) Hz, 1 H), 4.01 (dd, \( J = 11.6, 3.4 \) Hz, 1 H), 4.42–4.46 (m, 1 H), 4.47–4.53 (m, 1 H), 4.57 (dd, \( J = 9.5, 7.2 \) Hz, 1 H), 7.35 (dd, \( J = 7.6, 4.8, 0.9 \) Hz, 1 H), 7.73 (td, \( J = 7.7, 1.7, 1.0 \) Hz, 1 H), 7.93 (dt, \( J = 7.9, 1.2 \) Hz, 1 H), 8.64 (ddd, \( J = 4.8, 1.6, 0.9 \) Hz, 1 H).

\( ^{13}C \{^1H\} \) NMR (125 MHz, CDCl\(_3\)): \( \delta = 64.0 \) (CH\(_3\)), 68.6 (CH), 70.0 (CH\(_2\)), 124.0 (CH), 125.9 (CH), 136.8 (CH), 146.2 (C), 149.9 (CH), 164.5 (C).

HRMS (ESI, positive mode): \( m/z \ [M + Na^+] \) calcd for \( \text{C}_4\text{H}_7\text{N}_2\text{NaO}_7 \): 226.0705; found: 226.0699.

Analyzed for \( \text{C}_4\text{H}_7\text{N}_2\text{O}_7 \) (203.21); C, 53.20; H, 4.46; N, 34.37. Found: C, 53.16; H, 4.47; N, 34.29.

(\( \alpha \)-Hydroxymethyl)-2-(2-pyridyl)-4,5-dihydro-1H-imidazole (2)

A suspension of compound 10 (2.21 g, 10.9 mmol) and \( \text{Pd} / \text{C} \) (221 mg, 10\% w/w Pd) in MeOH (50 mL) was degassed (three cycles of freeze, pump and thaw) and then stirred under an atmosphere of H\(_2\) (1 atm) for 16 h at 23 °C. The mixture was filtered, then the solvent was removed under reduced pressure to yield compound 2 (1.82 g, 10.3 mmol, 95\%) as a yellow oil.

\( [\alpha]_{D}^{20} = -55.3 \) (c 1.11, MeOH).

IR (ATR): 3279 (br), 2927 (m), 2862 (m), 1659 (s), 1601 (m), 1566 (m), 1487 (m), 1456 (m), 1421 (m), 1371 (s), 1271 (m), 1189 (m), 1096 (m), 1045 (m), 979 (m), 801 (m) cm\(^{-1}\).

HRMS (ESI, positive mode): \( m/z \ [M + H^+] \) calcd for \( \text{C}_9\text{H}_8\text{N}_5\text{O} \): 226.0705; found: 226.0699.

Anal. Calcd for \( \text{C}_9\text{H}_8\text{N}_5\text{O} \) (177.21): C, 61.00; H, 6.26; N, 23.71. Found: C, 60.89; H, 6.57; N, 23.73.

(\( \gamma \)-Aryl-Butoxycarbonyl)-4-(hydroxymethyl)-2-(2-pyridyl)-4,5-dihydro-1H-imidazole (11)

K\(_2\)CO\(_3\) (2.70 g, 19.5 mmol) and Boc\(_2\)O (5.33 g, 24.4 mmol) were added to a solution of compound 9 (2.12 g, 10.4 mmol) in 15% aq KOH solution (25 mL) and the resulting mixture was heated to reflux for 3 h. The layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (50 mL). The combined organic layers were dried (MgSO\(_4\)) and filtered, and the solvent was removed under reduced pressure.


HRMS (ESI, positive mode): \( m/z \ [M + Na^+] \) calcd for \( \text{C}_6\text{H}_7\text{N}_2\text{NaO}_7 \): 300.1319; found: 300.1324; 

HRMS (ESI, positive mode): \( m/z \ [M + Na^+] \) calcd for \( \text{C}_6\text{H}_7\text{N}_2\text{NaO}_7 \): 300.1324; found: 300.1319.
IR (ATR): 2979 (w), 2931 (w), 2871 (w), 1708 (s), 1630 (w), 1588 (s), 1506 (s), 1455 (s), 1364 (s), 1271 (s), 1246 (s), 1237 (s), 1273 (s), 1163 (vs), 994 (w), 979 (w), 794 (w), 744 (w) cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 1.21 (s, 3 H), 1.78 (s, 3 H), 3.40 (dd, J = 11.9, 7.2 Hz, 1 H), 3.99–4.13 (m, 2 H), 4.27 (dd, J = 9.9, 4.1 Hz, 1 H), 4.05–4.18 (m, 2 H), 7.20–7.36 (m, 3 H), 7.46 (dt, J = 8.0, 0.9 Hz, 1 H), 7.72 (dd, J = 7.8, 1.8 Hz, 1 H), 7.77–7.81 (m, 2 H), 8.61 (ddd, J = 4.9, 1.5, 1.1 Hz, 1 H).

13C{1H} NMR (125 MHz, CDCl₃): δ = 21.8 (CH₂), 27.8 (CH₃), 50.0 (CH₂), 63.5 (CH), 82.1 (CH₃), 123.2 (CH), 124.3 (CH), 136.3 (CH), 148.9 (CH), 150.3 (C), 151.4 (C), 159.9 (C).

HRMS (ESI, positive mode): m/z [M + Na⁺] caletd for C₁₉H₂₃N₅O₈S: 454.1413; found: 454.1403.

References


4. For reviews, see: (a) Iwasa, S. Organometallics 2012, 31, 499.


